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(54) Title: ADHESIVE PRODUCTS

(57) Abstract

An adhesive product suitable for application to the body such as a wound dressing comprises a support layer, e.g. a conformable backing layer having on one side thereof a layer of an emulsion adhesive comprising residues of a copolymerisable emulsifier and wherein said adhesive coating contains a medicament. Suitable medicaments for topical use include antimicrobial agents such as povidone iodine, triclosan and chlorhexidine and its derivatives.

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ADHESIVE PRODUCTS

The present invention relates to adhesive products suitable for application to the human body and to processes for their preparation. More particularly the invention relates to adhesive products containing releasable medicaments.

Adhesive products suitable for application to the human body such as adhesive coated wound dressings often comprise a medicament, for example an anti-microbial agent, within the adhesive coating thereof to assist the wound healing process.

In the past considerable difficulties have been encountered in providing adhesive products with such a medicament containing adhesive coatings. It has been found that either the adhesive properties of the coatings are reduced substantially or the pharmacological activity of the medicament is reduced

eg because the medicament is not released. Adhesive products of this type have now been found in which adhesive coating exhibits both good adhesive properties and pharmacologically activity.

The use of antimicrobial agents with water based skin-contact adhesives has been proposed but only with limited success.

In European Patent Publication 0196459, there is disclosed adhesives containing polyhexamethylene biguanide (PHMB). Such adhesives may contain an anionic emulsifier. However, in comparative tests with other cationic antimicrobials PHMB was the only one shown to have acceptable antimicrobial activity with chlorhexidine having little or no activity.

We have how found that good antimicrobial activity can be had from water-based emulsion adhesives containing medicaments; including chlorhexidine, by employing an emulsifier for the adhesive which is copolymerised or reacted with the other adhesive components.

Accordingly the present invention provides an adhesive product suitable for application to the body

which product comprises a support layer having on one side thereof a layer of an emulsion adhesive comprising residues of a copolymerisable emulsifier and wherein said adhesive coating contains a medicament.

Suitable medicaments for use in the invention include medicaments for topical use such as antimicrobial agents. Favoured antimicrobial agents are water soluble. Such antimicrobial agents can include iodine compounds such as povidone iodine, triclosan and chlorhexidine and its derivatives.

Apt water soluble antimicrobial agents for use in the invention are chlorhexidine gluconate and acetate.

The amount of medicament in the adhesive coating of the adhesive product of the invention can suitably be from 0.1 to 10% by wt, desirably 0.1 to 5% by wt and can preferably be 0.15 to 2% by wt of the adhesive coating.

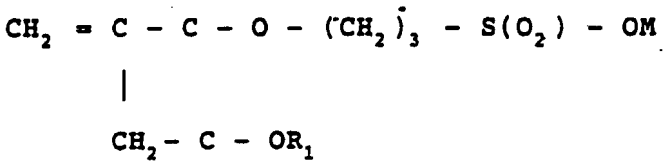
The adhesive used in the invention are typically water based adhesives and will normally and preferably be a pressure sensitive adhesive. The pressure sensitive adhesive will be an emulsion adhesive polymer containing residues of a vinyl monomer.

Preferred adhesives for use in the invention are acrylic pressure sensitive adhesives.

The copolymerisable emulsifier used in the invention therefore will normally be a surfactant containing a terminally unsaturated vinyl monomeric portion which can copolymerise with vinyl monomers such as acrylic monomers to form a pressure sensitive adhesive which is preferably an acrylic pressure sensitive adhesive. Such an acrylic pressure sensitive adhesive is desirably an acrylate or methacrylate based adhesive.

The copolymerisable emulsifier can be an anionic, cationic or non-ionic emulsifier. Favoured copolymerisable emulsifiers, however, will contain an anionic group such as a sulphonate.

Favoured adhesive products of the invention are those in which the emulsion adhesive polymer comprises residues of acrylic monomers containing 80 to 98.5% by weight of residues of alkyl esters of acrylic or methacrylic acid in which the alkyl group contains from 3 to 12 carbon atoms, from 0.1 to 20% by weight of residues of monoesters of methacrylic acid and 0.1 to 5% by weight of residues of a compound of the formula (I):



(I).

In which R_1 is a C_{10} - C_{14} alkyl radical and M is hydrogen, ammonia or an alkali metal.

Emulsion adhesive polymers of this type are in European Patent Application No. 0194881.

The alkyl radical in formula (I) may contain 12 carbon atoms and M can be sodium, that is the compound of formula (I) may be sodium mono-lauryl itaconoxy propane sulphonate.

Compounds of formula (I) have been found to be highly suitable copolymerisable emulsifiers for emulsion acrylic adhesives and can provide adhesive coatings of such adhesives which are less sensitive to water than coatings of similar emulsion adhesives containing a normally added non-polymerisable emulsifier.

The emulsion adhesive polymer used in the

invention can suitably comprise residues of one or more, for example two, alkyl esters of acrylic acid in which alkyl group contains 3 to 12 carbon atoms. Favoured alkyl esters of acrylic acid are those in which the alkyl group has 4 to 9 carbon atoms, such as n-butyl acrylate 2-ethylhexyl acrylate and other octyl acrylates. Preferred alkyl acrylates are n-butyl acrylate and 2-ethylhexyl acrylate.

Suitably the emulsion adhesive polymer used in the adhesive can comprise residues of one or more, for example two, monoesters of methacrylic acid. Suitable monoesters of methacrylic acid can be selected from a group consisting of a lower alkyl, hydroxylated or alkoxylated esters for example methyl methacrylate, n-buty methacrylate hydroxyethylmethacrylate and methoxyethylmethacrylate. Preferred monoesters include hydroxyethyl methacrylate, methyl methacrylate and n-butyl methacrylate.

The emulsion adhesive polymers for use in the invention can comprise 36 to 50% by weight of n-butyl acrylate residues, 39 to 59% by weight of 2-ethyl hexyl acrylate residues, 1 to 15% by weight of lower alkyl methacrylate residues, 0.3 to 5% by weight of hydroxyethyl methacrylate residues and 0.1 to 5% by weight of residues of a compound of formula (I). Lower

alkyl when used herein means an alkyl radical containing from 1 to 6 carbon atoms.

Emulsion adhesive polymers of this type can comprise 39 to 45% by weight of n-butyl acrylate residues, 47 to 49.5% by weight of 2-ethylhexyl acrylate residues, 5 to 10% by weight of lower alkyl methacrylate residues, 0.8 to 3% by weight of hydroxyethyl methacrylate residues and 0.1 to 1% by weight of residues of a compound of formula (I).

An example of an adhesive polymer for use in the invention comprises 44.5% by weight of n-butyl acrylate residues, 49.5% by weight of 2-ethylhexyl acrylate residues, 5% by weight of n-butyl methacrylate residues, 1% by weight of hydroxyethyl methacrylate residues and 0.2% by weight of sodium mono-lauryl itaconoxypropane sulphate.

The coating of emulsion adhesive of the adhesive product of the invention can suitably have a weight per unit area of 10 to 75g/m^2, desirably of 15 to 65g/m^2 and can preferably have a weight per unit area of 20 to 40g/m^2 for example 30g/m^2.

Adhesive product of the invention can favourably be a surgical or medical adhesive dressing. The

support layer therefore can suitably be a backing layer of a dressing of the invention, such back layers can be any of conformable backing layers used on conventional adhesive dressings. such backing layers can include woven and non-woven and knitted fabrics, flexible nets and flexible polymer films, including microporous films.

Preferred backing layers are moisture vapour transmitting films and in particular elastomeric moisture vapour transmitting films.

Favoured elastomeric moisture vapour transmitting films include those formed from polyether polyurethane, polyester polyurethane, hydrophilic polyurethane and polyester-polyether copolymers.

Suitable polyether polyurethanes are described in United States Patent No. 2899411. Suitable polyester polyurethanes are described in United States Patent No. 2871218. Apt polyester and polyether polyurethanes are known Estane (Trade Mark) available from B.F. Goodrich and in particular grades 5701, 5702, 5803, 5714F and 580201.

An apt polyester-polyether copolymer is known as Hytral 4056 available from Dupont.

Suitable hydrophilic polyurethane films for use in the inventions are disclosed in European Patent No. 91800.

The thickness of the films used for the backing layer can suitably be 9 to 80μm, more suitable 15 to 50μm and can preferably be 210 to 40μm for example 30μm.

Moisture vapour permeable dressings of the invention can suitably have a moisture vapour transmission rate of at least 300g/m^2/24h, more suitably at least 500g/m^2/24h and preferably at least 700g/m^2/24h at 37°C at 100% to 10% relative humidity difference. The moisture vapour permeable dressings of the invention suitably have a moisture vapour transmission (indicated) rate of at least 1200 gm/m^2/24h when in contact with water.

A suitable method of determining the upright moisture vapour transmission rate of the dressing of this invention is as follows. Discs of material under test are clamped over Payne Permeability Cups (flanged metal cups) using sealing rings and screw clamps. The exposed surface area of the test sample may be conveniently 10cm^2. Each cup contains approximately

10ml of distilled water. After weighing the cups are placed in a fan assisted electric oven maintained at 37 ± 1°C. The relative humidity within the oven is maintained at 10% by placing 1 KG of anhydrous 3-8 mesh calcium chloride on the floor of the oven. The cups are removed after 24 hours, allowed to cool for 20 minutes and re-weighed. The MVTR of the test material is calculated from the weight loss expressed in units of grams of weight per square metre per 24 hours.

A suitable method of determining the inverted moisture vapour transmission rate of the dressing of this invention is as follows. The method described above is employed except that the Payne Cups are inverted in the oven so that the water within the cups is in contact with the test material and in this case with the adhesive.

The adhesive product of the invention preferably have a releasable protector on the adhesive surface thereof. The protector used may be any of the flexible release materials conventionally used to protect the adhesive surface of dressings. Suitable protectors include those made from plastics films such polyethylene, polypropylene or unplasticised polyvinyl chloride films, paper sheets and coated paper sheets which have been treated with a release agent such as a

silicone resin.

Adhesive products in accordance with the invention can have a handle which is preferably removable attached to one or each of the opposing edge margins of the product material such as release coated paper or plastics film.

The handles can be attached either directly to the adhesive at opposed margins of the dressing indirectly by means of strips of adhesive tape which are preferably tearable to render the handles removable. Suitable dressings with removable handles of the type are disclosed in United Kingdom Patent Application No. 2157955. The handles can be adhered in a position in which they lie on top of the backing layer or preferably in a position where they lie alongside the backing layer.

The adhesive product can suitably be an adhesive surgical or medical dressing such as an adhesive wound dressing including a bandage, a first aid dressing, a burns dressing, a ulcer dressing, an IV or catheter dressing or a surgical incise drape.

Such dressings can be in the form of a sheet, tape or roll. Preferably the dressings of the

invention are sterile within a bacteria-proof package.

The adhesive dressings of the invention have an advantage over conventional adhesive dressing in that in use on a exuding wound the adhesive surface of the dressing can provide immediate and sustained delivery of a medicament such as an antimicrobial agent to the wound. Such dressings therefore may be effective in protecting wounds against pathogenic organisms.

Dressings of the invention which comprise an adhesive containing chlorhexidine gluconate have been found to have a high activity against Staphylococus Aureus.

In addition to their use as wound dressings, the dressings of the present invention may be employed, with advantage, as surgical incise drapes. Immediate release of the medicament such as chlorhexidine gluconate, provides rapid skin disinfection due to the bactericidal effect of the medicament. Sustained release provides a bacteristatic environment.

The dressings of the present invention, particularly those having high (inverted) moisture vapour permeability, for example greater than about 1400 $gm/m^2/24h$, can be used as IV dressings to protect,

for example, catheter implants.

In another aspect the invention provides a process for forming the adhesive product of the invention which comprises coating an aqueous solution of a medicament onto the exposed adhesive surface of an adhesive product which comprises a support layer having on one side thereof a coating of emulsion adhesive comprising residues of a copolymerisable emulsifier.

The materials used in the process of the invention can be the same as those used in the adhesive product of the invention.

Suitable adhesive products and methods of preparation for use in the process of the invention include those disclosed in the aforementioned European Patent Application No. 0194881.

The aqueous solution used in the process of the invention can be obtained by dissolving the medicament in water or a mixture of water and an water mixible organic solvent such as ethyl alcohol or isopropyl alcohol. Favoured solutions for use in the process comprise an aqueous solution of chlorhexidine salts such as the acetate or gluconate in suitable amounts in water or water - alcohol mixture. The percentage

weight ratio of 10 : 90 to 90 : 10 respectively, and preferably at a ratio of 20 : 80 to 80 : 20 respectively. The alcohol may be isopropyl alcohol at a weight ratio of for example, 30 : 70 to 50 : 50. The concentration of medicament in the aqueous solution can be adapted to the coated process and the weight per unit area desired.

The adhesive may be applied either as a continuous or discontinuous coating. In order to obtain dressings of high moisture vapour permeability eg greater than 1400 and preferably greater than 3000 pattern spread adhesives may be employed.

The aqueous solution of medicament can be coated on the exposed adhesive surface of the adhesive product by any suitable conventional coating method including spraying, doctor blade coating and roller methods such as a gravure roller printing method which is preferred.

After coating the medicament solution may be dried, for example by air drying or gentle heating.

It has been found that coating solutions containing 2 to 30% by weight of chlorhexidine gluconate can be coated by a gravure roller printing method and will provide dry coatings having desired

antimicrobial activity. Coating weights may be as high as 0.4 gm/m^2. However, coating weights (dry) of chlorhexidine gluconate as low as 0.040 g/m^2 have been found effective, and typically may be about 0.15 gm/m^2.

The invention will now be illustrated by reference to the following Examples.

Preparation of adhesive coated dressing

A acrylic adhesive emulsion containing residues of ethylhexyl acrylate (49.5% by wt) n-butyl acrylate (44.5% by wt, n-butyl methacrylate (5% by wt) hydroxy ethyl methacrylate (1% by wt) and sodium mono-lauryl itaconoxy propane sulphonate (0.2%) was prepared in the same manner as Example 1 of European Patent Application No. 0194881. The acrylic adhesive emulsion prepared above was thickened by addition of Prima ASE60 neutralised with ammoniam hydroxide and an antioxidant MONO & WSC (0.6% BY WT) added to the emulsion.

The emulsion was then coated onto a silicone release coated paper by means of a blade over flat bed coating head and dried in an oven at 110° and 5°C to give a dry adhesive coating weight per unit area of 30g/m^2. The adhesive coating was then transferred to a

polyether polyurethane (Estane 5712) film (30/m^2) by laminating under pressure the film and the adhesive coated release paper by pressing the layers between the nip of two pressure rollers.

Examples 1 to 4

Adhesive dressings of the invention

Adhesive dressings of the invention were prepared by coating the exposed adhesive surface of adhesive coated dressing samples prepared above with aqueous solutions containing different concentrations of chlorhexidine gluconate in water or water/isopropanol mixture by means of a gravure roller coating technique and allowed to air dry.

Example	Coating Solution			Coated C G		
	Water	:	Isopropanol	C G wt %	g/m_2	wt % of adhesive
1	28	:	70	2	0.041	0.14
2	24	:	70	6	0.18	0.43
3	40	:	50	10	0.22	0.73
4	100	:	0	20	0.40	1.33

C G - Chlorhexidine Gluconate, Subjective tests

indicated that the dressings of Example 1 to 4 has satisfactory adhesive properties.

Adhesive Dressing (Control)

An adhesive dressing control was prepared by coating the exposed adhesive surface of a adhesive coated dressing sample prepared above with water in same manner as the adhesive dressings of Examples 1 to 4.

Antimicrobial Test

Adhesive dressing samples of Example 1 to 5 and the Control were then subjected to a test to determine the antimicrobial activity of the exposed adhesive surface of these dressings. The test was carried out by the following procedure.

A number of 2.5 centimeter square samples were cut from the test dressings. Individual samples were placed in a petri dish. The samples were each inoculated with the test bacteria Staphylococus aureus. The adhesive surface of each sample was inoculated with about 10^5 bacteria, and the sample covered with a one 2.5cm glass square. The antibacterial activity of the chlorhexidine gluconate was inhibited after 0, 10 and

30 minutes, respectively by applying to the innoculum a Triptone-soya broth containing 3% by weight of lecothin and 2% by weight of a surfactant (Tween 80). The samples are cultured for 48 hours in an agar culture medium, and the surviving bacteria counted. The results are reported as a log decrease in bacteria from the "O" time to test time. For antimicrobial dressings or incise drapes, a 3 log reduction is desirable. A 3 log reduction equals a 99.9% kill of the bacteria originally present in the sample.

The results of the tests are as follows.

Example	Antimicrobial activity	
	Log Reduction	
	19 mins	30 mins
1	1.84	3.64
2	>4.14	>4.14
3	>4.14	>4.14
4	>4.14	>4.14
Control	-	0.15

The results show that the adhesive surface of adhesive dressings of Example 1 to 4 of the invention which contain medicament had satisfactory antibacterial

properties whereas the adhesive surface of the control adhesive dressing which did not contain medicament exhibited only poor antibacterial properties.

Example 5

The procedure of Examples 1 to 4 was followed to coat an adhesive coated film, prepared as described above, with chlorhexidine gluconate.

The adhesive coating weight on the polyethylene terephthlete film was 30 gsm and the chlorhexidine coating weight (dry) was 0.3 gsm. The chlorhexidine coating solution also contained a pink dye (Carmine).

Samples of the film together with samples of an adhesive coated but non-medicated control were then aged at 5°C, 20°C and 40°C for 4, 8 and 12 weeks, and after the elapsed time were inspected and tested to determine any changes in visual appearance (colour), adhesion and antimicrobial activity. The results are given below.

Adhesion

25mm wide samples of the aged films were adhered to a 180 Grit Blasted Satinised Stainless Steel plate

and the samples peeled back at 180°. The peel strength (N/m) at a peel rate of 300mm/min are given in Table 1.

Table 1

Ageing Time/Temp	Peel Strength (N/m)	
	Ex 5	Control
Initial	362	526
4 weeks/ 5°C	382	---
/20°C	350	---
/40°C	364	---
8 weeks/ 5°C	378	---
/20°C	371	---
/40°C	335	---
12 weeks/ 5°C	384	---
/20°C	374	---
/40°C	392	536

No loss of adhesion was observed upon ageing.

Microbiological Activity & Chlorhexidine Content.

The results of the antimicrobial test, as described above for sample of film according to this example, after 12 weeks of ageing and the Control are given in Table 2. The samples were also assayed for chlorhexidine content at the beginning and end of the

twelve week period and these values are also reported in Table 2.

Table 2

Ageing Temp.	Chlorhexidine Content		Log_{10} Reduction			
	% w/w	gsm	0 mins	5 mins	10 mins	30 mins
Initial	0.40	0.29	>4.06	>4.40	>4.40	>4.40
5°C	0.48	0.30	3.68	>4.40	>4.40	>4.40
20°C	0.44	0.29	3.30	>4.40	>4.40	>4.40
40°C	0.39	0.25	2.08	>4.40	>4.40	>4.40
Control	---	---	0	---	---	0.14

Claims

1. An adhesive product suitable for application to the body which comprises a support layer having on one side thereof a layer of an emulsion adhesive which adhesive comprises residues of copolymerisable emulsifier and wherein said adhesive layer contains a medicament.

2. A products according to claim 1 wherein the medicament is an antimicrobial agent.

3. A products according to claim 2 wherein the antimicrobial agent includes iodine compounds, triclosan or chlorhexidine or a derivative thereof.

4. A product according to claim 2 wherein the antimicrobial agent is water soluble.

5. A product according to claim 4 wherein the antimicrobial agent is chlorhexidine gluconate or chlorhexidine acetate.

6. A product according to any one of claims 1 to 5 containing medicament in an amount of from 0.1 to 10%

by weight of the adhesive.

7. A product according to any one of the preceding claims wherein the adhesive is a water based adhesive.

8. A product according to any one of the preceding claims wherein the adhesive is a pressure sensitive adhesive containing residues of a vinyl monomer.

9. A product according to claim 8 comprising the reaction product of an acrylic monomer and a surfactant containg terminal vinyl unsaturation.

10. A product according to any one of the preceding claims in the form of a medical or surgical dressing wherein the support layer comprises a conformable backing layer for the dressing.

11. A product according to claim 10 wherein the support layer comprises a moisture vapour transmitting elastomeric film.

12. A product according to claim 11 having a moisture transmission rate of at least 300 gm^{-2} 24 hr^{-1} at 37°C at 100% to 10% relative humidity.

13. A dressing suitable for the treatment of wounds and burns comprising a conformable backing layer having on one side thereof a layer of an emulsion adhesive which adhesive comprises (i) the reaction product of a copolymerisable emulsifier and a acrylic monomer and (ii) a medicament and wherein the adhesive surface is covered by a releasable protector.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/01481

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 L 15/44 A 61 L 15/58

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 L

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	WO,A,9101706 (SMITH & NEPHEW PLC) 21 February 1991, see page 8, lines 1-12; page 24, lines 15-24; page 25, lines 1-5 ---	1-13
X	WO,A,9101707 (SMITH & NEPHEW PLC) 21 February 1991, see page 7, line 1; page 24, lines 1-12 ---	1-13
Y	EP,A,0023395 (MINNESOTA MINING AND MANUFACTURING CO.) 4 February 1981, see claims ---	1-13
Y	EP,A,0194881 (SMITH AND NEPHEW ASSOCIATED COMPANIES PLC) 17 September 1986, see whole document (cited in the application) --- -/-	1-13

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
17-10-1992	20. 11. 92
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Mme Dagmar FRANK

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9201481 SA 63162

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/11/92
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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/11/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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